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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/954,954	10/21/97	SUMMERS N	2991/1

HM12/0503

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EXAMINER	
KEMMERER,E	
ART UNIT	**PAPER NUMBER**
1646	17

DATE MAILED: 05/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
08/954,954	Summers et al.
Examiner	**Group Art Unit**
Elizabeth C. Kemmerer	1646

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ☐ expires _____ months from the mailing date of the final rejection.

b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due two months from the date of the Notice of Appeal filed on *19 Apr 2000* (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *19 Apr 2000* has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

☒ The proposed amendment(s):

☒ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☐ will not be entered because:

☐ they raise new issues that would require further consideration and/or search. (See note below).

☐ they raise the issue of new matter. (See note below).

☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

☐ Applicant's response has overcome the following rejection(s):

☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:
Please see attachment.

☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: *1-14*

☐ The proposed drawing correction filed on _____ ☐ has ☐ has not been approved by the Examiner.

☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ .

☐ Other

Elizabeth C. Kemmerer

ELIZABETH C. KEMMERER
PRIMARY EXAMINER
ART UNIT 1646

ATTACHMENT TO ADVISORY ACTION

Applicant requested clarification that "claims 11, 2, 5, 6 and 10-14" appearing at p. 2, line 10 of the previous Office Action (Paper No. 13, 14 October 1999) was a typographical error and should have been "claims 1, 2, 5, 6 and 10-14". Applicant is correct.

Claims 4, 9 and 11-14 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments (p. 2, Paper No. 16, 19 April 2000) have been fully considered but are not deemed to be persuasive for the following reasons. Applicant argues that the Examiner failed to establish the clear issue of the rejection prior to the final rejection, and thus the finality of the previous Office Action should be withdrawn. The final Office Action was proper, because no new grounds of rejection were made. The basis for the rejection has been clear since Paper No. 9. In Paper No. 9 (29 April 1999), p. 3, it is clearly stated "it is impossible for the polypeptide sequence GlyGlyGlySer (SEQ ID NO: 123) to also be a polypeptide sequence selected from the group consisting of SEQ ID NOS: 124-130." Applicant's amendment to the claims did not resolve this issue, and the following Office Action was properly made final. The suggestion for correction made in Paper No. 9 should have been sufficient for one skilled in the art to identify a remedy. It was misconstrued in a way that could not have been predicted by the Examiner, and thus a more thorough suggestion was made in

Paper No. 13. Suggestions for correction are not required elements of the rejection. The required element was to set forth the issue, which was done in Paper No. 9. Thus, Paper No. 13 was properly made final.

It is noted that the claims still have not been amended to correct the issue.

Claims 1, 5 and 10-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Lin for reasons of record.

Applicant asserts that the Examiner ignored one of the two requirements for determination of an appropriate opening site, namely, that the new termini can be formed without disrupting a region critical for protein folding and desired activity. Applicant also refers to Goldberg et al., 1989 as supporting this statement. Applicant then asserts that the Examiner has failed to point to teachings in the cited prior art regarding sites in EPO critical for protein folding. This is not found to be persuasive. Pastan et al. do indeed state that selection of the opening site is important to the permutein's activity, and that the opening site must not interrupt secondary structure critical to folding or final three dimensional conformation. However, the ultimate test of this is to test whether the resulting protein has activity. Pastan et al. provide guidance regarding selection of an opening site to achieve this for proteins such as EPO wherein homologs of the protein are known; i.e., an opening site in regions not showing highly conserved sequences (see column 8, lines 45-50). Lin provides detailed information regarding the conserved regions of EPO, thus providing the information essential to choosing an appropriate opening site that will not adversely affect protein folding or activity. After

choosing such opening sites, the resulting permutein could then be routinely screened to confirm that the relevant activity was retained.

Applicant argues that the rejection improperly establishes an obvious to try standard. Specifically, Applicant characterizes Pastan et al. ('599) as limited to general statements that circular permutation can be applied to other ligands. Applicant urges that Pastan et al. provides no factual support for any of the other ligands in the cited prior art beyond that which is claimed in Pastan et al. Applicant characterizes Pastan et al.'s disclosure as extremely limited. Applicant focuses on the Examiner's statement that Pastan et al. discloses that fusion proteins of circular permuteins often have highly specific binding affinities. Applicant urges that Pastan et al. only presents biological data for two circular permuteins of IL-4. Applicant characterizes the relevant literature as evidencing the unpredictable nature of circular permutation. Applicant points to the file history of Pastan et al. as showing that the Examiner stated that the art of circular permutation was unpredictable. Applicant concludes that there was no reasonable expectation of success. This is not found to be persuasive. First of all, it would be inappropriate for the Examiner to comment on the prosecution history of Pastan et al. beyond restating the official record, as every patent must be presumed to be valid unless proven otherwise in a court of law, and the instant Applicant and Attorney are unrelated to those in Pastan et al. Pastan et al. will not be reexamined during the course of prosecution for this application. Before the disclosure of Pastan et al., the skilled artisan would not have expected that a drastic structural alteration of a protein, such as circular permutation, would have resulted in an active variant of the protein. The very issuance of Pastan et al., a pioneering patent, has matured this art.

Not only did Pastan et al. disclose that circular permutation could result in active variants, they also provided guidance regarding selection of opening sites and the routine nature of making circular permuteins and screening for active variants. In view of Pastan et al., the Examiner chose not to reject the instant claims under 35 U.S.C. §112, first paragraph for lack of enablement regarding opening sites, because it was her determination that it would not constitute undue experimentation to construct all of the recited species and then test them for the desired activity, and it is not impermissible to have a claim which encompasses inoperative species. However, by the same token, it would not constitute undue experimentation for the person of ordinary skill in the art, having the teachings of the cited prior art in hand, to determine which circularly permuted forms of EPO would have agonist activity. The art teaches both the desirability of making such circularly permuted proteins, as well as providing guidance as to what sites would be desirable as permutation sites. If applicants would like to continue to assert that the results of making such circularly permuted molecules are unpredictable, they are advised that similarly, evidence of unexpected results, such as data demonstrating that the particularly claimed species have a particular activity, would be given considerable weight in overcoming this rejection.

Applicant points to column 8, lines 45-53 of Pastan et al. as suggesting trying one parameter and then the opposite, and failing to teach which parameters are critical.. this is not found to be persuasive. Applicant has misconstrued to meaning of this passage in Pastan et al. Pastan et al. teach that, where homologs of a protein are known and an alignment can be constructed, regions that do not show conserved sequence identity are good candidates for opening sites. This is the parameter

to consider *when no permuteins of the protein have previously been tested.* However, *if a permutein of one of the proteins has been successfully made wherein an opening site is in a conserved region,* then that site is also likely to work in the other homologs. This section of Pastan et al. does not translate to "try one thing and then the opposite." Rather, it provides guidance on selecting an opening site *depending on what is already known about the protein.*

Applicant criticizes Lin as providing limited information, and asserts that there are inconsistencies between the different suggestions made by Pastan et al., such that no true guidance has been given to the skilled artisan regarding selection of any one opening site as preferable to another, but that the combined teachings are merely an invitation to experiment. If the claimed invention were limited to only a few opening sites, this would be found to be persuasive. However, the claims refer to any one of 67 opening sites. Considering EPO is only about 165 amino acids in length, the claims indicate that more than 40% of the residues are appropriate as an opening site. It has been determined that no rejection of the instant claims under 35 U.S.C. §112, first paragraph for lack of enablement regarding opening sites was necessary, because it was determined that it would not constitute undue experimentation to construct all of the recited species and then test them for the desired activity, and it is not impermissible to have a claim which encompasses inoperative species. However, by the same token, it would not constitute undue experimentation for the person of ordinary skill in the art, having the teachings of the cited prior art in hand, to determine which circularly permuted forms of EPO would have agonist activity. The art teaches both the desirability of making such circularly permuted proteins, as well as providing guidance as to what sites would be

desirable as permutation sites. If applicants would like to continue to assert that the results of making such circularly permuted molecules are unpredictable, they are advised that similarly, evidence of unexpected results, such as data demonstrating that the particularly claimed species have a particular activity, would be given considerable weight in overcoming this rejection.

Applicant concludes by arguing that the prior art does not indicate which parameters are critical, and which of the many choices is likely to be successful. Applicant argues that the Examiner has improperly rejected the claims on the basis of a general method of making wherein specific molecules are claimed, citing *In re Bell*. Applicant concludes that only an obvious to try standard has been met. This is not found to be persuasive. First, it is respectfully pointed out that the fact pattern of *In re Bell* is completely different than the instant fact pattern. The issue in *Bell* was whether or not a gene sequence was obvious when part of the corresponding protein sequence was known. In the instant case, a full length fusion protein was known, and an altered version of one of the components in the context of a full length fusion protein was known. The instant facts concern a simple swapping of fully characterized parts. Furthermore, the rejection is maintained because it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion proteins of Pastan et al., including the DNA and methods for making such, by substituting for the cytokines disclosed therein the EPO disclosed by Lin. One of ordinary skill in the art would have been motivated to make circularly permuted forms of EPO disclosed by Lin by the disclosure of Pastan et al. that such circularly permuted proteins are expected to retain or have improved binding properties to the receptor to which they bind, as compared to the non-permuted

forms. Thus, the claimed invention as s whole was very clearly *prima facie* obvious over the prior art.

Claims 1-4 and 6-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Lin and further in view of Chaudhary et al. and Cousens et al. for reasons of record.

Applicant argues that the linkers of Chaudhary et al. and Gearing et al. are in the context of fusion proteins and that the requirements for linking fusion proteins versus circular permuteins are different. This is not found to be persuasive, because the structures of the linkers disclosed by Chaudhary et al. and Cousens et al. overlap those which Applicant indicates as appropriate for the instant invention. It cannot be held that a compound is both suitable and unsuitable for a given application.

This application still contains claims 15-22 drawn to an invention nonelected with traverse in Paper No. 4. A complete reply to the final rejection should have included cancellation of nonelected claims or other appropriate action (37 CFR 1.144), as set forth at p. 8 of the previous Office Action (Paper No. 13, 14 October 1999). See also MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D., can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

ECK
May 2, 2000